

Remarks/Arguments

Claims 1, 4, 29-36, 42, 43, 49-62, 66-82, 84 and 85 are pending in the application. Claims 2, 3, 5-28, 37-41, 44-48, 63-65, 83, 86 and 87 were previously canceled. No amendments to the claims are made herein. Accordingly, no new matter has been added.

Interview

Applicants would like to thank the Examiner for an interview, completed on May 27, 2011, during which the Office Action mailed on March 1, 2011 was discussed. Specifically, we discussed the Amendment to the Specification, filed on June 4, 2009. It was agreed that the Applicants would submit a substitute specification to be filed with the response to the Office Action. Accordingly, a substitute specification is included herewith.

Further, with respect to the 35 U.S.C. §103(a) rejection below in view of Nelson *et al.* (U.S. Patent No. 7,056,902), Applicants pointed out that the compounds from Nelson selected by the Examiner include hydrogen at the 4-position while the compounds described in the claims include dialkylamino moieties at the 4-position. Moreover, the 7- and 9-positions of the compounds from Nelson (e.g., 7-dimethylamino-9-aryl substituted compounds) are distinct from those of the claimed compounds (e.g., 7-furanyl/7-thienyl-9-hydrogen). The Examiner agreed that these structural differences were sufficient to overcome the current rejection.

With respect to the 35 U.S.C. §103(a) rejection below in view of WO01/19784 and U.S. Patent 7,045,507/WO02/072031, Applicants pointed out that the treatment of malaria was recited in the rejected claims. The Examiner agreed that this was sufficient to overcome the current rejection.

Finally, with respect to the double patenting rejections, the Examiner stated that these rejections would be withdrawn in view of the above and in view of the effective filing date of the instant application.

Accordingly, Applicants thank the Examiner and request that the rejections described herein be withdrawn in accordance with our discussion.

Substitute Specification

Applicants note the Examiner's statement that the Applicants' Amendments to the Specification, submitted on June 4, 2009, have not been entered as no reasons were provided for the amendments (*see* Office Action at pp. 2 and 16).

As discussed in our interview, dated May 27, 2011, Applicants provide a substitute specification herewith. Specifically, Applicants provide the following:

Exhibit A: A Clean Version of the Substitute Specification;

Exhibit B: A Marked Version of the Substitute Specification; and

Statement under 37 CFR 1.125(b).

Applicants note that the Formulae in Table 1 have been enlarged for clarity. Specifically, Table 1 has been enlarged for publication purposes. No changes have been made to the text of the application. No markings have been made to the specification. As such, the text of the Marked Version is the same as the Clean Version. Accordingly, Applicants request that the Examiner enter the substitute specification into the record.

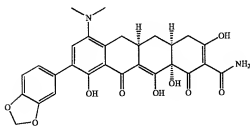
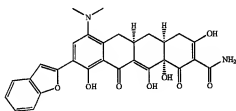
Amendment to Specification

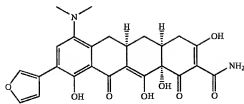
Applicants have amended the Related Applications section of the substitute specification as shown herein. The priority claim was present in the application as filed and was reflected on the filing receipt mailed on February 23, 2004. Accordingly, Applicants request that the Examiner enter the amendment into the record.

35 U.S.C. §103(a)

Claims 1, 4, 29-36, 42, 43, 49-62, 66-82, 84 and 85 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Nelson *et al.* (U.S. Patent No. 7,056,902).

According to the Examiner, Nelson describes compounds such as:





(hereinafter referred to as “Compound 3”)

(see Office Action at p. 5). The Examiner stated that Nelson describes the use of these compounds in treating malaria. *Id.* The Examiner further noted that the instant claims differ from Nelson in that they are of different generic scope (see Office Action at p. 10). Thus, the Examiner concluded that the claimed invention would have been *prima facie* obvious (see Office Action at pp. 10-11). Applicants traverse the rejection.

Proof of obviousness based on structural similarity requires clear and convincing evidence that a medicinal chemist of ordinary skill would have been motivated to select and then to modify a prior art compound (e.g., a lead compound) to arrive at a claimed compound with a reasonable expectation that the new compound would have similar or improved properties compared with the old. See Daiichi Sankyo Co. v. Matrix Laboratories, Ltd. (Fed. Cir. September 9, 2010). In keeping with the flexible nature of an analysis of obviousness, the motivation to select and modify a lead compound is not required to be explicit in the art.

Further, in Daiichi Sankyo Co. v. Matrix Laboratories, Ltd., the Federal Circuit commented on the issue of lead compound selection, stating that its cases “illustrate that it is the possession of promising useful properties in a lead compound that motivates a chemist to make structurally similar compounds.” The court continued, explaining that “attribution of a compound as a lead compound after the fact must avoid hindsight bias; it must look at the state of the art *at the time the invention was made* to find a motivation to select and then modify a lead compound to arrive at the claimed invention” (emphasis in original). Thus, “proving a reason to select a compound as a lead compound depends on more than just structural similarity, but also knowledge in the art of the functional properties and limitations of the prior art compounds,” and therefore, “[p]otent and promising activity in the prior art trumps mere structural relationships.”

That is, in order to show obviousness, the skilled artisan in light of the totality of the prior art, must have been motivated, first, to select a prior art compound and, second, to modify the compound to arrive at the claimed compound with a reasonable expectation that the new compound would have similar or improved properties compared with the old. The Examiner has failed to describe any motivation to select Compound 1, 2 or 3, from Nelson, for further modification.

As discussed in our interview described above, the instant claims are drawn towards methods of treating or preventing malaria comprising administering a 7-substituted tetracycline compound, including 4-dialkylamino and 9-hydrogen moieties, and related compositions. Compounds 1-3 cited by the Examiner are 9-substituted-4-dedimethylamino tetracycline compounds, including a 7-dimethylamino moiety. The Examiner also cited claims 1 and 11 of Nelson (*see* Office Action at pp. 5-6). Claims 1 and 11 of Nelson similarly describe 9-substituted-4-dedimethylamino tetracycline compounds where the 7-position is dialkylamino. The instant claims recite compounds that are distinct from those cited by the Examiner in at least three positions, namely, the 4-, 7- and 9-positions of the tetracycline structure. Thus, contrary to the Examiner's statement that the **"invention is the selection of the prior art compounds,"** the compounds recited in the instant claims are not encompassed by the compounds and claims cited by the Examiner (*see* Office Action at p. 10).

Further, Nelson describes a genus encompassing 4-dedimethylamino tetracycline compounds and discloses many specific tetracycline compounds in Table 2. The Examiner has provided no reason to select any of Compounds 1-3 from those listed in Nelson.

Further, even if *arguendo* Compound 1, Compound 2 or Compound 3 were selected (Applicants submit they would not be), there is no motivation to modify the selected compound to reach the compounds recited in the claims.

As described above, the compounds cited by the Examiner are distinct from the claimed compounds in at least three positions (*i.e.*, the 4-, 7- and 9-positions) of the tetracycline structure. The Examiner provides no reason or motivation to modify any of Compounds 1-3 to include a dialkylamino group at the 4-position. Further, the Examiner provides no reason or motivation to modify any of Compounds 1-3 to include a furanyl, benzofuranyl, thienyl or benzothienyl moiety at the 7-position. The Examiner provides no reason or motivation to modify any of Compounds 1-3 to include a hydrogen atom at the 9-position. Finally, the Examiner provides no reason or motivation to modify any of Compounds 1-3 at each of the 4-, 7- and 9-positions to arrive at the claimed invention.

The structures of Compounds 1-3 each include more than 10 positions that can be readily modified with one or more chemical moieties. The Examiner provides no motivation to choose which of the more than 10 positions to modify, much less which specific chemical modification to make, much less to modify with the currently claimed 4-, 7- and 9-position substituents to arrive at the claimed compounds.

Thus, the Examiner has failed to describe any motivation to select Compound 1, 2 or 3, from Nelson, for further modification. As a result, the claimed methods and related compositions would not have been *prima facie* obvious in view of Nelson.

Based on the foregoing, Applicants respectfully request reconsideration and withdrawal of the rejection.

Claims 81 and 82 have been rejected under 35 U.S.C. §103(a) as being unpatentable over WO01/19784 ("the '784 application") and U.S. Patent 7,045,507/WO02/072031 ("the '507 patent").

According to the Examiner, the '784 application describes compositions with structurally similar tetracycline compounds as those embraced by the instant claims (*see* Office Action at p. 11). The Examiner also stated that the '507 patent describes compositions with structurally similar tetracycline compounds as those embraced by the instant claims. *Id.* Thus, the Examiner concluded that the claimed compositions would have been *prima facie* obvious (*see* Office Action at pp. 12-13). Applicants traverse the rejection.

Applicants note the Examiner's statement that the previous 35 U.S.C. §103(a) rejection in view of the '784 application and the '507 patent has been withdrawn with respect to claims 1, 4, 29-36, 42, 43, 49-62, 66-80, 84 and 85. Specifically, Applicants argued that it was not *prima facie* obvious to use the compounds recited in the claims to treat malaria. *See* Applicants' Response filed September 23, 2010 at pp. 17-19. However, the Examiner has maintained the rejection with respect to claims 81 and 82, drawn to pharmaceutical compositions (*see* Office Action at pp. 16-17). Specifically, the Examiner noted that even where the reference does not teach the same use of a composition, different intended uses are not distinguishable in terms of the composition. *Id.* at p. 17.

As discussed in our interview described above, claims 81 and 82 are drawn towards pharmaceutical compositions comprising an effective amount of a tetracycline compound to treat malaria. Applicants assert that claims 81 and 82 are not merely drawn to compositions, but recite compositions for the treatment of malaria. As a result, compositions used for treating the non-malarial disorders described in the cited references are distinguishable from the claimed pharmaceutical compositions. As a result, claims 81 and 82 are not *prima facie* obvious in view of the '784 application and the '507 patent.

Based on the foregoing, Applicants respectfully request reconsideration and withdrawal of the rejection.

Double Patenting

Claims 1, 4, 29-36, 42, 43, 49-62, 66-82, 84 and 85 have been provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-28 of copending U.S. Application No. 11/490,867. Applicants traverse this provisional double patenting rejection.

Applicants recognize that the Examiner has noted Applicants' traversal of this provisional double patenting rejections in view of M.P.E.P. at § 804 section I, subsection B1 (see Office Action at p. 17). Accordingly (and as discussed in our interview described above), Applicants request withdrawal of this provisional double patenting rejection upon indication of allowable subject matter in the instant application.

Claims 1, 4, 29-36, 42, 43, 49-62, 66-82, 84 and 85 have been provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over copending U.S. Application Nos. 11/039,230; 11/490,867; and 11/348,608. Applicants traverse these provisional double patenting rejections.

With respect to U.S. Application No. 11/490,867, the arguments made above with respect to this application is incorporated herein. As such, Applicants request withdrawal of this provisional rejection.

With respect to U.S. Application Nos. 11/039,230 and 11/348,608, Applicants recognize that the Examiner has noted Applicants' traversal of these provisional double patenting rejections in view of M.P.E.P. at § 804 section I, subsection B1 (see Office Action at p. 17). Accordingly (and as discussed in our interview described above), Applicants request withdrawal of these provisional double patenting rejections upon indication of allowable subject matter in the instant application.

Claims 1, 4, 29-36, 42, 43, 49-62, 66-82, 84 and 85 have been rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-12 of U.S. Patent No. 7,056,902. Applicants traverse these provisional double patenting rejections.

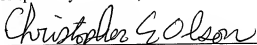
Applicants note that U.S. Patent No. 7,056,902 is also cited in a 35 U.S.C. §103(a) rejection above. As such, Applicants incorporate herein the arguments made above with respect to the 35 U.S.C. §103(a) rejection in view of U.S. Patent No. 7,056,902. Accordingly

(and as discussed in our interview described above), Applicants request withdrawal of this double patenting rejection.

Conclusion

Applicants submit that this paper is fully responsive and that the application is in condition for allowance. Should any questions arise concerning the application, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,



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